Significant Prognostic Factors for Vogt-Koyanagi-Harada Disease in the Early Stage

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This study identified possible prognostic signs in the acute stage of Vogt-Koyanagi-Harada (VKH) disease in a retrospective chart review of all patients diagnosed with VKH disease between 1991 and 2001. Those who were diagnosed more than 1 month after the onset of ocular symptoms were excluded. Data recorded included age, sex, clinical features, systemic manifestations, recurrence, treatment, complications, and final visual acuity. Exudative retinal detachment was ranked into 3 grades (grade 1: within peripapillary 3 disc diameters and arcade; grade 2: larger than grade 1 but no inferior retinal detachment; grade 3: inferior or total retinal detachment). Of the 31 patients, 19 were males and 12 were females. Mean age at presentation was 38.55 ± 10.63 years. The mean follow-up period was 33.09 months. Extraocular manifestations were present in 17 cases. Four patients had at least one complication, including cataract in seven eyes and glaucoma in one eye. Forty-nine eyes (79%) had a final visual acuity of 6/12 or better. Final visual acuity was significantly better in younger patients ($p = 0.023$) and those who had less extensive retinal detachment ($p = 0.006$), no pigmentary change ($p = 0.008$) and no complications ($p = 0.030$). The visual prognosis of VKH disease is variable, though generally favorable. In the acute stage, the extent of retinal detachment may be an important risk factor for visual outcome. Further study of this factor as an indicator for treatment is necessary.

Key Words: prognosis, retinal detachment, Vogt-Koyanagi-Harada disease
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Vogt-Koyanagi-Harada (VKH) disease is a chronic bilateral granulomatous panuveitis with involvement of the central nervous system and auditory and integumentary systems [1,2]. The exact cause of the disease is uncertain, but T-lymphocyte-mediated autoimmunity directed against melanocytes is likely to play an important role [3–6]. There seems to be a genetic predisposition, because specific human leukocyte antigen (HLA) types have been reported to be associated with the disease [7–11]. VKH disease is more prevalent in certain racial and ethnic groups, particularly in Asian individuals and certain Latin-American groups [1, 12–14]. The visual prognosis is generally favorable, yet significant vision loss occurs in some cases. Irreversible vision loss is typically caused by complications that arise as a result of the disease or its treatment, including cataract, glaucoma, choroidal neovascularization, and subretinal fibrosis. A number of factors are reported to be related to these complications, such as age at onset, worse visual acuity at presentation, rapid tapering of steroid, and interval between symptom onset and diagnosis [15–22]. It would be helpful to find prognostic factors in the early stage of VKH disease that could be used as a treatment guideline. In this study, we tried to identify possible prognostic factors in the early stage of VKH disease.

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Materials and Methods

We performed a retrospective chart review of all patients diagnosed with VKH disease in our ophthalmic departments

between 1991 and 2001. Diagnosis of VKH disease is based on the features typically present at the stage of disease during which the patients are examined; other uveitis conditions are excluded by history, examination, and ancillary testing. The revised criteria for VKH disease were applied retrospectively to patients with a diagnosis of endogenous uveitis [23]. Patients who were diagnosed and treated before visiting our departments or who were followed up for less than 6 months were excluded. In order to catch all ocular signs in the early stage of VKH disease, we excluded those who visited more than 1 month after the onset of ocular symptoms.

Charts were reviewed for demographic data, clinical features, systemic manifestations, recurrence, treatment, complications, and final visual acuity. Ophthalmologic examinations included slit lamp biomicroscopy, intraocular pressure, indirect ophthalmoscopy, contact lens biomicroscopy, and fundus fluorescein angiography. A cataract was defined as any change in the normally clear media of the native lens that resulted in loss of vision, caused a change in refractive error, or obscured visualization of the fundus. Glaucoma was defined as a sustained elevation of the intraocular pressure necessitating the use of medical and/or surgical therapy. Choroidal neovascularization was defined as growth of new blood vessels within the subretinal space or subretinal pigment epithelial space, as demonstrated by fluorescein angiography. Although not previously reported, exudative retinal detachment was empirically ranked into one of three grades (grade 1: within peripapillary 3 disc diameters and arcade; grade 2: larger than grade 1 but no inferior retinal detachment; grade 3: inferior or total retinal detachment) (Figures 1–3).

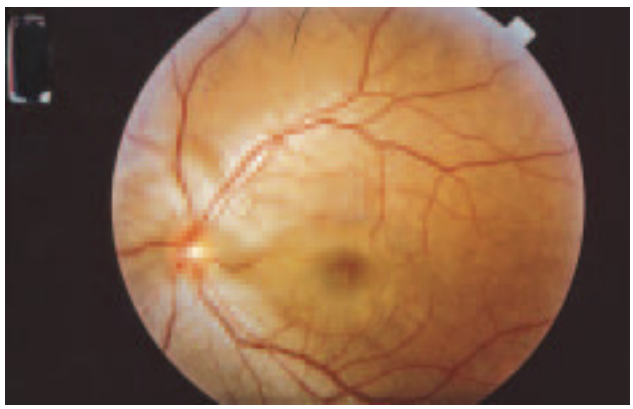

Figure 1. *A 28-year-old male diagnosed with Vogt-Koyanagi-Harada disease 2 days after onset of ocular symptoms. There were no central nervous system or integumentary symptoms. Ophthalmic manifestations included a silent anterior chamber and grade 1 exudative retinal detachment in both eyes. The final visual acuity was 6/6 after treatment. No complications developed during follow-up.*

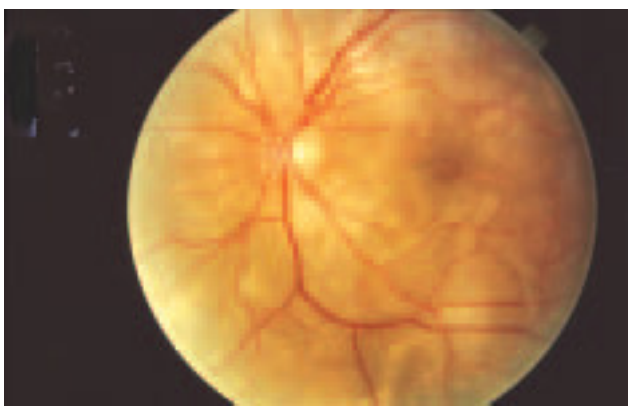

Figure 2. *A 51-year-old female, with prodromal central nervous system symptoms, diagnosed with Vogt-Koyanagi-Harada disease 3 days after the onset of ocular symptoms. Ophthalmic manifestations included anterior uveitis and grade 2 exudative retinal detachment in both eyes. The final visual acuity was 6/6.7 after treatment. No complications developed during follow-up.*

Statistical analysis

The Chi-squared test was used to compare the proportions between two or three groups. Fisher's exact test was used when one or more expected values were less than 5 in the 2 × 2 tables. If sample variances were comparable, sample means between two or three groups were compared using a *t* test or one-way ANOVA. If sample variances were not comparable, sample mean ranks between two groups were compared using the Mann-Whitney U test.

Results

There were 31 patients with mean age at presentation of 38.55 ± 10.63 years (range, 20–63 years); 19 (61.3%) were male. The mean follow-up period was 33.09 months. At initial presentation, ocular manifestations were usually symmetrical in both eyes. Anterior uveitis was present in 12 cases (38.7%), vitreous haziness in 15 (48.4%), exudative retinal detachment in 31 (100%), and neurologic or auditory manifestations in 16 (51.6%). The extent of exudative retinal detachment did not correlate with interval between symptom onset and diagnosis ($p = 0.172$, Spearman's rank correlation test). At the time of the last follow-up, cutaneous manifestations were present in one patient (3.2%) and sunset glow fundus or other ocular depigmentation in 22 eyes. Overall, four patients (7 eyes) developed cataracts and one developed glaucoma (1 eye with both cataract and

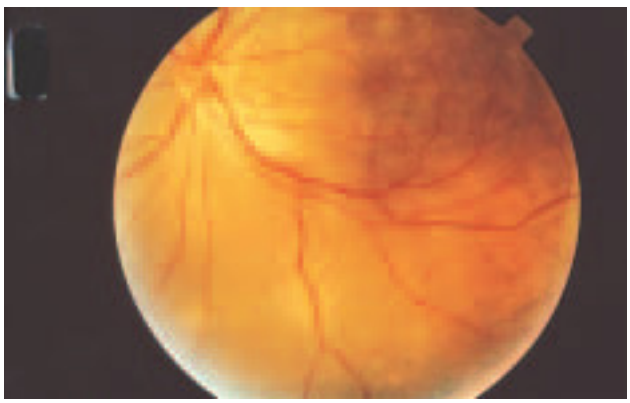

Figure 3. *A 51-year-old male diagnosed with Vogt-Koyanagi-Harada disease 1 week after onset of ocular symptoms. There were no central nervous system or integumentary symptoms. Ophthalmic manifestations included mild vitreous cell reaction and grade 3 exudative retinal detachment in both eyes. The final visual acuity was 6/30 after treatment. There was one recurrence during follow-up. The fundus had a sunset glory appearance in both eyes at the last visit.*

glaucoma); no choroidal neovascularization was found at the last follow-up.

Twenty-seven patients were diagnosed and treated within 2 weeks after the onset of ocular symptoms, while four patients were diagnosed and treated between 2 weeks and 1 month. Treatment consisted of oral corticosteroid (1 mg/kg/day) and topical steroid eye drops in 17 patients, and megadose methylprednisolone (250 mg intravenously every 6 hours for 3 days) plus oral and topical steroid in 14 patients. Corticosteroid was tapered gradually over 6 months. Cytotoxic agents were used as adjuvant therapy in three cases that responded poorly to corticosteroid. After treatment, recurrence occurred in seven patients (22.6%). Forty-nine eyes (79%) had a final visual acuity of 6/12 or better.

Among patients treated within 1 month of the onset of ocular symptoms, those with extraocular manifestations had a significantly longer interval between symptom onset and treatment than those without ($p = 0.007$). There were no significant differences in age and gender distribution, recurrence, ophthalmic features, presence of complications, or final visual acuity between these two groups (Table 1). For patients who developed complications, there were no

Table 1. Characteristics of patients with and without extraocular manifestations

	With extraocular manifestation (n = 17)	Without extraocular manifestation (n = 14)	p
Mean age ± SD, yr	40.47 ± 10.95	36.21 ± 10.12	0.274*
Gender			0.138†
Male, n (%)	8 (47.1)	11 (78.6)	
Female, n (%)	9 (52.9)	3 (21.4)	
Interval between symptom onset and treatment ± SD, wk	1.70 ± 1.50	0.76 ± 0.71	0.007*
Anterior chamber reaction			1.000†
Yes	6	5	
No	11	9	
Vitreous reaction			0.722†
Yes	9	6	
No	8	8	
RD grading ± SD	1.88 ± 0.78	1.86 ± 0.77	0.953*
Recurrence			
Yes	4	3	
No	13	11	
Presence of complications			
Cataract	2	2	1.000†
Glaucoma	1	0	1.000†
CNV	0	0	
Final visual acuity ≥ 6/12	14	9	0.412†

*Mann-Whitney U test; †Fisher's exact test. SD = standard deviation; RD = retinal detachment; CNV = choroidal neovascularization.

significant differences in the age and gender distribution, interval between symptom onset and diagnosis, anterior uveitis, or extraocular manifestations. The extent of exudative retinal detachment ($p = 0.023$) and recurrence ($p = 0.028$) were significantly related to the development of complications (Table 2). The extent of exudative retinal detachment was the only significant factor in the development of recurrence ($p = 0.048$) (Table 3).

A number of factors were examined in this study to identify those that were associated with a worse outcome. The mean age was significantly greater among patients with final vision worse than 6/12 compared with patients with final vision of 6/12 or better ($p = 0.023$) (Table 4). There was no difference in the gender distribution, irrespective of the presence of extraocular manifestations. There was a difference in the incidence of recurrence with visual outcome, but this did not reach significance ($p = 0.056$). A significant difference was detected in patients with the complication of cataract, though not glaucoma, which might be due to the limited number of cases. Of the ophthalmic features in the early stage, anterior chamber reaction and vitreous reaction were not significantly related to visual outcome; however, the extent of exudative retinal detachment ($p = 0.006$) was significantly different between the group with final vision better than 6/12 and the group with final vision worse than 6/12. The presence of ocular pigmentary changes also correlated with poor visual outcome ($p = 0.008$) (Table 4). In patients who were diagnosed and treated within 2 weeks after the onset of ocular symptoms, the extent of exudative retinal detachment ($p = 0.023$) and the presence of ocular pigmentary changes ($p = 0.029$) were also significantly correlated with visual outcome (Table 5). Contrary to the data in Table 4, patients with anterior chamber reaction tended to have a final vision of 6/12 or better ($p = 0.039$).

Discussion

Patients with VKH disease may have varied outcome with regard to final visual acuity. The treatment of choice varies around the world. Usually, the principles of therapy of VKH disease are to suppress the initial intraocular inflammation with early and aggressive use of systemic corticosteroid therapy. Cytotoxic/immunosuppressive agents are needed in refractory cases [2]. Most patients

Table 2. Factors for the development of complications

	Complications ($n = 4$)	No complications ($n = 27$)	p
Mean age ± SD, yr	37.75 ± 13.33	38.67 ± 10.47	0.875*
Gender			
Male, *n* (%)	4 (100)	15 (55.6)	
Female, *n* (%)	0	12 (44.4)	
Interval between symptom onset and treatment ± SD, wk	1.25 ± 0.50	1.11 ± 0.32	0.657*
Anterior chamber reaction			0.630†
Yes	2	9	
No	2	18	
Vitreous reaction			1.000†
Yes	2	13	
No	2	14	
RD grading ± SD	2.75 ± 0.50	1.74 ± 0.71	0.023‡
Extraocular manifestation			1.000†
Yes	2	15	
No	2	12	
Recurrence			0.028†
Yes	3	4	
No	1	23	

*t test, unpaired; †Fisher's exact test; ‡Mann-Whitney U test. SD = standard deviation; RD = retinal detachment.

Table 3. Factors affecting recurrence

	Recurrence (n = 7)	No recurrence (n = 24)	p
Mean age ± SD, yr	35.14 ± 13.93	39.54 ± 9.60	0.344*
Gender			0.676†
Male, n (%)	5 (71.4)	14 (58.3)	
Female, n (%)	2 (28.6)	10 (41.7)	
Interval between symptom onset and treatment ± SD, wk	1.14 ± 1.28	1.74 ± 1.27	0.283*
Anterior chamber reaction			1.000†
Yes	3	8	
No	4	14	
Vitreous reaction			0.685†
Yes	4	11	
No	3	13	
RD grading ± SD	2.43 ± 0.79	1.71 ± 0.69	0.048‡
Extraocular manifestation			1.000†
Yes	4	13	
No	3	11	

*t test, unpaired; †Fisher's exact test; ‡Mann-Whitney U test. SD = standard deviation; RD = retinal detachment.

respond and regain vision. However, significant vision loss resulting from complications occurs in spite of intensive treatment [13–15,18]. Treatment without massive corticosteroid therapy was reported with good visual outcome [24]. Considering the side effects of massive corticosteroid therapy, treatment without it would be useful in some cases with a benign course. In order to decide which patient will have a benign course, factors in the acute stage of VKH disease need to be recognized to guide treatment.

A number of factors are reported to be related to poor visual outcome, including the presence of complications, age at onset, worse visual acuity at presentation, rapid tapering of steroid, interval between symptom onset and diagnosis, and a greater number of recurrences [15–22]. The development of complications, recurrence, and tapering of steroid are not good indicators at an early stage. Age is a controversial factor. Ohno and associates reported that the younger the age at disease onset, the worse the final visual acuity [15]. Tabbara et al also found poor results in pediatric patients [16]. However, Rathinam et al reported that children 16 years of age or younger with VKH disease generally do well [17]. In Read et al's report, a statistically significant association existed between poor final visual acuity and greater age at onset. Our data support the suggestion by Read et al that greater age at onset is associated with poor visual outcome [18]. In their report, eyes with a better visual acuity at presentation were more likely to have a better visual acuity at final follow-up [18]. As usual, early diagnosis and prompt treatment is the key to success. Fujioka et al noted that if patients were not treated within 2 weeks, longer steroid therapy was required [19]. Mondkar and associates reported that visual prognosis was good in patients presenting within 1 month of onset of symptoms [20]. Bouchenaki et al found that the inflammation was more easily controlled in patients who were diagnosed in less than 2 weeks [21]. Since we included only patients who were diagnosed within 1 month after ocular symptom onset, the influence of the interval factor could not be evaluated in this study. However, it seems that interval influenced the outcome, as some factors differed between patient groups who were diagnosed within 1 month or within 2 weeks. The significance of age and complications diminished in patients who were diagnosed and treated within 2 weeks. This implies that the earlier patients were treated, the less likely they were to develop complications, even in the older age group. Like all other diseases, early diagnosis and prompt treatment is the key to prevent complications and, hence, to better outcome.

Table 4. Factors affecting final visual acuity

	Final VA ≥ 6/12 (49 eyes)	Final VA < 6/12 (13 eyes)	*p*
Mean age ± SD, yr	37.10 ± 10.84	44.00 ± 7.34	0.023*
Gender			0.062†
Male, *n* (%)	27 (55.1)	11 (84.6)	
Female, *n* (%)	22 (44.9)	2 (15.4)	
Interval between symptom onset and treatment ± SD, wk	1.25 ± 1.31	1.38 ± 1.18	0.754‡
Anterior chamber reaction			0.337†
Yes	20	3	
No	29	10	
Vitreous reaction			1.000†
Yes	24	6	
No	25	7	
RD grading ± SD	1.63 ± 0.73	2.31 ± 0.75	0.006*
Extraocular manifestation			0.220†
Yes	29	5	
No	20	8	
Recurrence			0.056†
Yes	8	6	
No	41	7	
Presence of complications	3	4	0.030†
Cataract	3	4	0.030†
Glaucoma	0	1	0.210†
CNV	0	0	
Ocular depigmentation			0.008†
Yes	13	9	
No	36	4	

*Mann-Whitney U test; †Fisher's exact test; ‡*t* test, unpaired. VA = visual acuity; SD = standard deviation; RD = retinal detachment; CNV = choroidal neovascularization.

Hayasaka et al reported that the VK form of VKH disease (severe anterior uveitis and exudative retinal detachment) was more resistant to treatment, requiring more than 200 mg of intravenous prednisone therapy daily [25]. In our study, the extent of exudative retinal detachment correlated significantly with the development of recurrence or complications and final visual outcome. Although not previously reported, we graded the extent of exudative retinal detachment according to our empirical experience that patients with less exudative retinal detachment had better outcome. Our results provide quantitative evidence to support this speculation. Nevertheless, there was no significant difference between anterior chamber reaction and the development of complications or recurrence or final visual outcome. Moreover, patients diagnosed within 2 weeks with anterior chamber reaction seemed to have better visual outcome than those with no anterior chamber reaction. This was contradictory to Hayasaka et al's report. We cannot explain the discrepancy in the influence of anterior chamber reaction between patients diagnosed within 2 weeks and those diagnosed within 1 month. A large-scale study is necessary to solve this puzzle.

In conclusion, our study showed that the extent of exudative retinal detachment might be an important prognostic factor for visual outcome and might be a useful treatment guideline in the early stage of VKH disease.

Acknowledgments

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Table 5. Prognostic factors for visual outcome in patients treated early (≤ 2weeks)

	Final VA ≥ 6/12 (43 eyes)	Final VA < 6/12 (11 eyes)	*p*
Mean age ± SD, yr	38.28 ± 10.96	42.18 ± 6.40	0.236*
Gender			0.087†
Male, *n* (%)	21 (48.8)	9 (81.8)	
Female, *n* (%)	22 (51.2)	2 (18.2)	
Anterior chamber reaction			0.039†
Yes	18	1	
No	25	10	
Vitreous reaction			0.736†
Yes	20	4	
No	23	7	
RD grading ± SD	1.60 ± 0.69	2.18 ± 0.75	0.023*
Extraocular manifestation			0.095†
Yes	25	3	
No	18	8	
Recurrence			0.185†
Yes	6	4	
No	37	7	
Presence of complications	3	2	0.266†
Cataract	3	2	0.266†
Glaucoma	0	1	0.204†
CNV	0	0	
Ocular depigmentation			0.029†
Yes	11	7	
No	32	4	

*Mann-Whitney U test; †Fisher's exact test. VA = visual acuity; SD = standard deviation; RD = retinal detachment; CNV = choroidal neovascularization.

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早期原田病之預後指標

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探討原田病急性期之可能預後指標。回顧性研究自 1991 年至 2001 間診斷為原田病的病例。排除發病一個月以上才診斷者。病歷摘錄包括年齡、性別、臨床表徵，全身性表徵、復發、治療、合併症及最終視力。漿液性視網膜範圍依離視神經距離分 3 級(第一級：於視神經周 3 個視神經盤直徑遠。第二級：比第一級範圍廣，但無下部之網膜剝離。第三級：下部或全部視網膜剝離者)。共收集 31 例包括 19 位男性 12 位女性。平均年齡 38.55 ± 10.63 歲。平均追踪期為 33.09 個月。有 17 例有眼外表徵。4 例有至少一項合併症，包括 7 眼白內障，一眼青光眼。49 眼(79%)最終視力達 6/12 以上。統計結果發現年輕者(p = 0.023)，網膜剝離範圍較少(p = 0.006)，無色素性變化(p = 0.008)或發生合併者(p = 0.030)有較佳之視力預後。原田病之視力預後一般不錯，但變數仍多，在急性期，滲液性視網膜剝離的範圍有可能是重要的預後指標。是否可作為治療之指引需待更一進步的研究。

關鍵詞：預後、視網膜剝離、原田病

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